Nonlinear controller synthesis for HIV dynamics based on SOS

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ABSTRACT Nowadays antiretroviral therapy is widely used to cut down the viral burden and cut off a few infection sources in clinical medicine for Human Immunodeficiency Virus (HIV) infected patients, and a lot of evidence have shown that a massive coverage with antiretroviral therapy has already acquired a series of contributions and successes to save life and popularize preventive knowledge. Based on the HIV dynamic model, this paper designs a feedback controller to adjust the concentration values of CD4+T cell, CD8+T cell and viral load in HIV dynamic model to a healthy condition asymptotically. The HIV dynamic model is expressed in the form of a polynomial system and then the control law, as the appropriate drug dosage usually applied in the medical therapy, is designed to suppress the reproduction of the HIV virus and improve the production rate of healthy cell in vivo, simultaneously. According to the polynomial Lyapunov theory and sum of squares (SOS) technique, the conditions for the controller synthesis are proposed. The simulation experimental results can be testified the availability of the proposed method.

INDEX TERMS Human Immunodeficiency Virus, antiretroviral therapy, polynomial Lyapunov theory, sum of squares.

I. INTRODUCTION

In the world today, especially in many sub-Saharan African nations and a number of impoverished nations in Asia and South America, epidemic diseases are still acting as a dark role to seriously influence and restrict indigenous social stability and public hygiene development. Moreover, in the long run, this is not only a regional problem but also is a very serious cosmopolitan problem that has been released by some international organizations, academic reports, public media or social media all over the world. Acquired immunodeficiency syndrome (AIDS) is one of the fulminating infectious diseases that threatens the global human health so that it may be causing a series of unpredictable social and public health events. Nowadays Human Immunodeficiency Virus (HIV) infection issue has been more or less obstructing global society's stability and progress to a certain extent. This is the main reason why the early-stage epidemic prevention and therapeutic measures are very meaningful [1-3]. Generally speaking, the infection mechanism of HIV is that virus invades CD4+T cells in the human immune system, namely, HIV attacks and infects healthy CD4+T cells to let the healthy CD4+T cells to be infected cells. Because of the abovementioned factors, the population of CD4+ T cells decreases that will result in healthy situations to slowly slip into the human immunodeficiency situation, it means that the patient is tardily losing the protection of the defense shield in the body. Modern world still exists a few difficulties in the field of HIV therapy due to the clinical vaccines without high efficiency to protect humankind. Currently, clinical medicine employs highly active antiretroviral therapy (HAART), which usually includes several different antiretroviral drugs to be synthetically used, to treat patients. Reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) are the typical choices for some time henceforth [4-7]. Although it has an incredible success to treat HIV infection via clinical therapeutic study, but all known drugs or techniques cannot eliminate all viruses in the human body to touch an aim to cure infected patients yet.

Mathematic dynamic modeling methods based on clinical experimental data hold many important significances in clinical therapy and medical study. Mathematic modeling method for HIV dynamics study can easily reveal the

variations and phenomena of an integrated infection process in the human body. Thereby, a suitable HIV dynamic model can help us to indirectly understand the details of the virus infection mechanism, evolution, natural death and clearance. Thereby, on the basis of the previous presentation, mathematic modeling method can help scientists or researchers further reveal several new features of the HIV infection, or supply a new way to evaluate the worth of some medical study programs.

In the last decades, a lot of time and energy had been devoted to studying the dynamics of HIV infection model or other infectious diseases. A compartmental model was established for HIV infection among men who have sex with men, which is used to evaluate the efficiency of antiretroviral therapy (ART) in cutting off the spread of HIV infection [8]. On account of many developed or developing therapeutic methods or drugs for HIV/AIDS, some mathematic models had been formed for the previous studies such as via exploring three types of CD4+ cells: uninfected cells, infected cells in the incubation period and infected cell production to obtain a differential equation model [9]. Some papers focus on the optimal scheduling [10] for drug dosage to drive body condition of the patient to a steady healthy state. Nowadays, there exist many papers with different control designs to improve their contributions in the biomedical study field. Some control methods for the issues of drug dosage scheduling have been used to treat HIV infection. While most of these studies desired the completed states for the proposed control, even more, some of them cannot capture the performances and changes of the entire dynamic process. In addition, some papers used linearization or T-S fuzzy approach to build the original HIV model. It is noted that the nonlinear HIV system directly represented by the polynomial nonlinear system is more precise with respect to linearization approach [11], or T-S fuzzy system [12]. Because using the method of [11], the linearized system is only similar to the original nonlinear HIV system that means it cannot represent the original model completely. Moreover, if we use T-S fuzzy system to represent the HIV model, the computational burden will increase due to a number of fuzzy rules as well. Here, a feedback control approach based on SOS has been proposed to handle the drug scheduling of a polynomial HIV model system. On the other hand, the recent research prefers to resolve certain questions about the polynomial nonlinear system directly rather than use linearized approximate model. Therefore, design and analysis via SOS technique have become the new tendency. Previously linear matrix inequality (LMI) has gotten lots of attention. A core characteristic of the LMI-based approaches owns simple and effective features as compared with other control approaches. However, the LMI-based approaches still look into certain design problems which cannot be represented perfectly in accordance with LMI [13] or cannot solve solutions conveniently via LMI. Thus, SOS-based approaches are considered as a novel road to solve some problems such as

it can efficiently and directly describe nonlinear polynomial systems or design nonlinear polynomial controllers in control theory. It means that the SOS-based approaches can well express the models without via linearizing or other approaches to obtain proximate models for solving approximate results as compared with the original models. Certainly, it is well-known that the developed SOS-based approaches [13-17] supplied much more extensive or relaxed results than the other existing control approaches. However, there exist few academic papers on SOS-based feedback control design for directly studying a polynomial HIV model system. For this purpose, we present this approach in this paper to explain how it can work to enforce the states of the patient recovering to the healthy states.

The article structure is shown as follows: In section 2, some preliminary knowledge about the HIV model is presented. In section 3, the control problem to be dealt with is described. Section 3 is the main result and its proof. In section 4, a numerical experiment and its simulation are shown in this section. In the last section, the conclusion is given.

II. PRELIMINARY AND PROBLEM DESCRIPTION

The model of HIV dynamics to be considered is as follows

$$\dot{\bar{x}}_1 = p_1\left(x_{10} - \bar{x}_1\right) - p_2\bar{x}_1\bar{x}_3$$
$$\dot{\bar{x}}_2 = p_3\left(x_{20} - \bar{x}_2\right) + p_4\bar{x}_2\bar{x}_3 \qquad (1)$$
$$\dot{\bar{x}}_3 = \bar{x}_3\left(p_5\bar{x}_1 - p_6\bar{x}_2\right)$$

where $\bar{x} = \begin{bmatrix} \bar{x}_1 & \bar{x}_2 & \bar{x}_3 \end{bmatrix}^T$ is the state vector which contains $\bar{x}_1$ (CD4+T cells), $\bar{x}_2$ (CD8+T cells) and $\bar{x}_3$ (viral load, i.e., it corresponds to 10^7 times measurement for the viral load in $copies/ml$). Moreover, p_1, p_2, ... , and p_6 are some positive constants whose description and values are listed in Table 1.

TABLE 1
DESCRIPTION OF PARAMETERS AND STATE VARIABLES

Variable and parameter	Description	Value
$\bar{x}_1$	CD4+T cells population	N/A
$\bar{x}_2$	CD8+T cells population	N/A
$\bar{x}_3$	HIV viral load	N/A
p_1	CD4+T cells death rate	0.25
p_2	CD4+T cells infection rate	50
p_3	CD8+T cells death rate	0.25
p_4	CD8+T cells growth rate in response to viral load growth rate	10
p_5	Viral load growth rate	0.01
p_6	Viral load clearance rate	0.006
x_{10}	CD4+T cell's unperturbed equilibrium value	1000
x_{20}	CD8+T cell's unperturbed equilibrium value	550

It is known that the system (1) has two equilibrium points, one is

$$\overline{x}_1^* \triangleq x_{10} = 1000 \,, \ \overline{x}_2^* \triangleq x_{20} = 550 \,, \text{ and } \overline{x}_3^* = 0 \qquad (2)$$

and the other is

$$\overline{x}_1^* = \frac{p_1 p_4 p_5 x_{10} + p_2 p_3 p_6 x_{20}}{p_1 p_4 p_5 + p_2 p_3 p_5} = 442$$

$$\overline{x}_2^* = \frac{p_1 p_4 p_5 x_{10} + p_2 p_3 p_6 x_{20}}{p_1 p_4 p_6 + p_2 p_3 p_6} = 736 \qquad (3)$$

$$\overline{x}_3^* = \frac{p_1 p_3 \left(p_5 x_{10} - p_6 x_{20} \right)}{p_1 p_4 p_5 x_{10} + p_2 p_3 p_6 x_{20}} = 0.006.$$

Let the right-hand side of (1) be denoted by f, where

$$f = \begin{bmatrix} p_1 \left(x_{10} - \overline{x}_1 \right) - p_2 \overline{x}_1 \overline{x}_3 \\ p_3 \left(x_{20} - \overline{x}_2 \right) + p_4 \overline{x}_2 \overline{x}_3 \\ \overline{x}_3 \left(p_5 \overline{x}_1 - p_6 \overline{x}_2 \right) \end{bmatrix}. \qquad (4)$$

In order to analyse the local stability of the equilibrium points, let us consider the eigenvalues of the Jacobian matrix $F = \partial f / \partial \overline{x}$, where

$$F = \begin{bmatrix} -p_1 - p_2 \overline{x}_3 & 0 & -p_2 \overline{x}_1 \\ 0 & -p_3 + p_4 \overline{x}_3 & p_4 \overline{x}_2 \\ p_5 \overline{x}_3 & -p_6 \overline{x}_3 & p_5 \overline{x}_1 - p_6 \overline{x}_2 \end{bmatrix}. \qquad (5)$$

With the aid of parameter values in Table 1, at the equilibrium point (2), $\left(\partial f / \partial \overline{x} \right)\big|_{\overline{x}^*=(2)}$ has the eigenvalues (-0.25, -0.25, 6.7). It means that (2) is an unstable equilibrium point. At the equilibrium point (3), $\left(\partial f / \partial \overline{x} \right)\big|_{\overline{x}^*=(3)}$ has the eigenvalues (-0.2498+1.2616i, -0.2498-1.2616i, -0.2531) which is a stable equilibrium point. It is noted that (2) is corresponding to a healthy individual and (3) is for an infected individual [18].

The point (2) represents the equilibrium of the healthy condition which is the desired state of the system to be approached. Now we have changed the state variables as the form (6)

$$x = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} = \begin{bmatrix} \overline{x}_1 - x_{10} \\ \overline{x}_2 - x_{20} \\ \overline{x}_3 \end{bmatrix} \qquad (6)$$

so that the new model will be presented as (7)

$$\dot{x}_1 = -p_1 x_1 - p_2 \left(x_1 + x_{10} \right) x_3$$
$$\dot{x}_2 = -p_3 x_2 + p_4 \left(x_2 + x_{20} \right) x_3 \qquad (7)$$
$$\dot{x}_3 = x_3 \left[p_5 \left(x_1 + x_{10} \right) - p_6 \left(x_2 + x_{20} \right) \right]$$

where $x_1 + x_{10} = \overline{x}_1 > 0$, $x_2 + x_{20} = \overline{x}_2 > 0$ and $x_3 = \overline{x}_3 \geq 0$.

The state trajectories of HIV model simulation without any control for the system (7) with initial conditions $\overline{x}_1(0) = 1000 \ cells/mm^3$, $\overline{x}_2(0) = 550 \ cells/mm^3$ and $\overline{x}_3(0) = 0.0001$ (corresponding to $1000 \ copies/ml$) are shown in Fig. 1. It is seen that if an infected person has not any drug treatment, the equilibrium point $\begin{bmatrix} 442 & 736 & 0.006 \end{bmatrix}^T$ is the final state of the infected patient. On the other hand, if a person's state is staying at the unstable equilibrium point (2) continuously, the person keeps being healthy. However, if any state is disturbed to be away from the equilibrium point (2) a little, then the person's health will be deteriorated if no drug treatment. It is known that a patient with HIV can live with no apparent symptom for a long time, even if there is not any drug treatment. But, unfortunately, this condition is just an asymptotic stability with the HIV virus, hence the patient is still going to death finally. Therefore, we need to apply a drug treatment (or say, design a control law) to make the infected patient's states approach the healthy equilibrium point (2) and keep there forever.
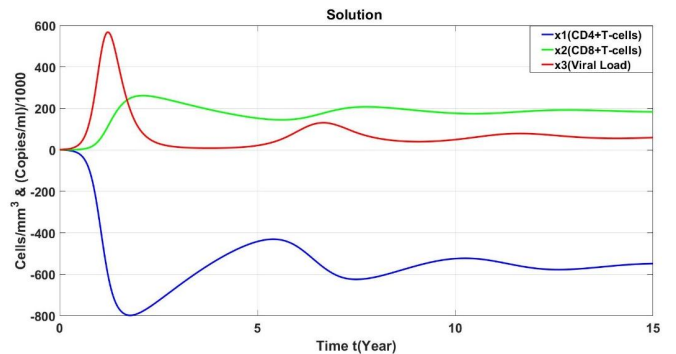

Figure 1. The state responses of the system without control u.

In general, the drug therapy u is added in the third equation of (7), then the system becomes

$$\dot{x}_1 = -p_1 x_1 - p_2 \left(x_1 + x_{10} \right) x_3$$
$$\dot{x}_2 = -p_3 x_2 + p_4 \left(x_2 + x_{20} \right) x_3 \qquad (8)$$
$$\dot{x}_3 = x_3 \left[p_5 \left(x_1 + x_{10} \right) - p_6 \left(x_2 + x_{20} \right) \right] - u.$$

Based on the above exposition and analysis, the main concern in this study is how to design a controller u (so-called drug dosage) for the system (8) such that the infected condition can be adjusted to the healthy condition asymptotically. Or it is said that the control will make the state vector x in (8) approach zero asymptotically.

III. MAIN RESULT

Let (8) be rewritten as

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} -p_1 & 0 & -p_2 x_1 - p_2 x_{10} \\ 0 & -p_3 & p_4 x_2 + p_4 x_{20} \\ p_5 x_3 & -p_6 x_3 & p_5 x_{10} - p_6 x_{20} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ -1 \end{bmatrix} u, \quad (9)$$

then, (9) can be represented in a polynomial nonlinear system

$$\dot{x} = A(x)x + B(x)u \quad (10)$$

where $x \in \Re^{3 \times 1}$, $u \in \Re^{1 \times 1}$, $A(x)$ and $B(x)$ are polynomial matrices as follows

$$A(x) = \begin{bmatrix} -p_1 & 0 & -p_2 x_1 - p_2 x_{10} \\ 0 & -p_3 & p_4 x_2 + p_4 x_{20} \\ p_5 x_3 & -p_6 x_3 & p_5 x_{10} - p_6 x_{20} \end{bmatrix}, \quad B(x) = \begin{bmatrix} 0 \\ 0 \\ -1 \end{bmatrix}. \quad (11)$$

Now the main task is to design the feedback controller u

$$u = K(x)x \quad (12)$$

where $K(x) \in \Re^{1 \times 3}$ is a polynomial gain matrix such that the closed loop system with (8) and (12) will be asymptotically stable. Or it is said that we proceed to design a suitable drug therapy treatment as (12) such that the healthy equilibrium point is achieved asymptotically.

Before starting the design work, some definitions and lemmas need to be stated first since they will be used in the proof of the main theorem.

Definition 1 [19, 20]**:** A multivariable polynomial $\rho(x) = f(x_1, \ldots, x_n)$, where $x \in \Re^n$, is an SOS if there exist polynomials $f_1(x), \ldots, f_m(x)$, such that

$$\rho(x) = \sum_{i=1}^{m} f_i^2(x). \quad (13)$$

Lemma 1 [12, 19, 20]**:** Let $\rho(x)$ be a polynomial in $x \in \Re^n$ of degree $2d$. In addition, let $Z(x)$ be a column vector whose entries are all monomials in x with a degree no greater than d. Then $\rho(x)$ is a sum of squares (SOS) if and only if there exists a positive semidefinite matrix Q such that

$$\rho(x) = Z^T(x)QZ(x). \quad (14)$$

For any polynomial matrix $\Lambda(x)$, let $\Lambda_k(x)$ be defined as the k-th row of $\Lambda(x)$. Now the following theorem is given to provide the conditions for the feedback control (13) design.

Theorem 1: For the HIV dynamic system (8) with the control (12), the states will approach zero asymptotically if there exist a polynomial matrix $M(x) \in \Re^{1 \times 3}$ and a symmetric polynomial matrix $P(\tilde{x}) \in \Re^{3 \times 3}$, such that

$$v^T \left(P(\tilde{x}) - \varepsilon_1(x)I \right) v \text{ is an SOS,} \quad (15)$$

$$-v^T \left[P(\tilde{x})A^T(x) + M^T(x)B^T(x) + A(x)P(\tilde{x}) + B(x)M(x) \right. \\ \left. -\sum_{k \in \Gamma} \frac{\partial P(\tilde{x})}{\partial x_k} A_k(x)x + \varepsilon_2(x)I \right] v$$

is an SOS, (16)

and

$$K(x) = M(x)P^{-1}(\tilde{x}) \quad (17)$$

where $\tilde{x}$ is a vector composed of elements x_k, $k \in \Gamma$, $\Gamma = \{ k | B_k(x) = 0, x \in \Re^{3 \times 1} \}$ and the polynomials $\varepsilon_1(x) > 0$ and $\varepsilon_2(x) > 0$ for $x \neq 0$. $v \in \Re^{3 \times 1}$ is a vector that is independent of x.

Proof: Consider a candidate of polynomial Lyapunov function for the closed-loop system (8) and (12) as

$$V(x) = x^T P^{-1}(\tilde{x})x, \quad (18)$$

where $P^{-1}(\tilde{x})$ is a polynomial matrix. Substituting (17) and (12) into (10), we have

$$\dot{x} = A(x)x + B(x)M(x)P^{-1}(\tilde{x})x. \quad (19)$$

The derivative of $V(x)$ is

$$\dot{V}(x) = \dot{x}^T P^{-1}(\tilde{x})x + x^T P^{-1}(\tilde{x})\dot{x} + x^T \dot{P}^{-1}(\tilde{x})x. \quad (20)$$

Meanwhile, $\dot{P}^{-1}(\tilde{x})$ can be rewritten as follows

$$\dot{P}^{-1}(\tilde{x}) = \frac{dP^{-1}(\tilde{x})}{dt} = \frac{\partial P^{-1}(\tilde{x})}{\partial x} \frac{\partial x}{\partial t} = \sum_{k=1}^{3} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \dot{x}_k. \quad (21)$$

Substituting (19) into (21) yields

$$\dot{P}^{-1}(\tilde{x}) = \sum_{k=1}^{3} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \Big[A_k(x)x$$
$$+ \big(B(x)M(x)P^{-1}(\tilde{x})\big)_k x \Big]$$
$$= \sum_{k=1}^{3} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big[A_k(x)x \big] \qquad (22)$$
$$+ \sum_{k=1}^{3} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big(B(x)M(x)P^{-1}(\tilde{x})\big)_k x,$$

where $\dot{x}_k = A_k(x)x + \big(B(x)M(x)P^{-1}(\tilde{x})\big)_k x$ that is obtained from (19). Based on Definition 2, in the system (9), $k \in \Gamma = \{1, 2\}$, it means that $\tilde{x} = (x_1, x_2)$. If $k \notin \Gamma$, then $k = 3$. Therefore, it is easy to see that $\partial P^{-1}(\tilde{x}) / \partial x_3 = 0$. Furthermore, since $B_k(x) = 0, k = 1, 2$, then $\big(B(x)M(x)P^{-1}(\tilde{x})\big)_k$ is a zero vector for $k = 1, 2$. Therefore, it is obvious that

$$\sum_{k=1}^{3} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big(B(x)M(x)P^{-1}(\tilde{x})\big)_k x = 0 \qquad (23)$$

and

$$P^{-1}(\tilde{x}) = \sum_{k=1}^{3} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big[A_k(x)x \big]$$
$$= \sum_{k \in \Gamma} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big[A_k(x)x \big]. \qquad (24)$$

Hence, from (23) and (24), we have

$$\dot{P}^{-1}(\tilde{x}) = \sum_{k \in \Gamma} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big[A_k(x)x \big] \qquad (25)$$

and (20) becomes

$$\dot{V}(x) = \dot{x}^T P^{-1}(\tilde{x})x + x^T P^{-1}(\tilde{x})\dot{x}$$
$$+ x^T \left(\sum_{k \in \Gamma} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big[A_k(x)x \big] \right) x. \qquad (26)$$

Substituting (19) into (26) obtains

$$\dot{V}(x) = \big(A(x)x + B(x)M(x)P^{-1}(\tilde{x})x\big)^T P^{-1}(\tilde{x})x$$
$$+ x^T P^{-1}(\tilde{x})\big(A(x)x + B(x)M(x)P^{-1}(\tilde{x})x\big)$$
$$+ x^T \left(\sum_{k \in \Gamma} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big[A_k(x)x \big] \right) x$$
$$= x^T \Big[\big(A(x) + B(x)M(x)P^{-1}(\tilde{x})\big)^T P^{-1}(\tilde{x})$$
$$+ P^{-1}(\tilde{x})\big(A(x) + B(x)M(x)P^{-1}(\tilde{x})\big) \qquad (27)$$
$$+ \left(\sum_{k \in \Gamma} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big[A_k(x)x \big] \right) \Big] x$$
$$= x^T \Big[A^T(x)P^{-1}(\tilde{x}) + P^{-1}(\tilde{x})M^T(x)B^T(x)P^{-1}(\tilde{x})$$
$$+ P^{-1}(\tilde{x})A(x) + P^{-1}(\tilde{x})B(x)M(x)P^{-1}(\tilde{x})$$
$$+ \left(\sum_{k \in \Gamma} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big[A_k(x)x \big] \right) \Big] x.$$

It is known that the system (9) will be asymptotically stable if $\dot{V}(x)$ is negative. From (27), if let the following equation hold, then $\dot{V}(x)$ will be negative.

$$-\Big[A^T(x)P^{-1}(\tilde{x}) + P^{-1}(\tilde{x})M^T(x)B^T(x)P^{-1}(\tilde{x}) +$$
$$P^{-1}(\tilde{x})A(x) + P^{-1}(\tilde{x})B(x)M(x)P^{-1}(\tilde{x}) \qquad (28)$$
$$+ \left(\sum_{k \in \Gamma} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big[A_k(x)x \big] \right) \Big] > 0.$$

Pre and post multiplying (28) with $P(\tilde{x})$ obtains

$$-\Big[P(\tilde{x})A^T(x) + M^T(x)B^T(x)$$
$$+ A(x)P(\tilde{x}) + B(x)M(x) \qquad (29)$$
$$+ P(\tilde{x})\left(\sum_{k \in \Gamma} \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} \big[A_k(x)x \big] \right) P(\tilde{x}) \Big] > 0.$$

Because $P(\tilde{x})$ is an invertible polynomial matrix, $P(\tilde{x})P^{-1}(\tilde{x}) = I$. Here, differentiating both sides of $P(\tilde{x})P^{-1}(\tilde{x}) = I$ with respect to x_k, it yields

$$P^{-1}(\tilde{x}) \frac{\partial P(\tilde{x})}{\partial x_k} P^{-1}(\tilde{x}) = -\frac{\partial P^{-1}(\tilde{x})}{\partial x_k}. \qquad (30)$$

Then

$$\frac{\partial P(\tilde{x})}{\partial x_k} = -P(\tilde{x}) \frac{\partial P^{-1}(\tilde{x})}{\partial x_k} P(\tilde{x}). \qquad (31)$$

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From (31), (29) can be rewritten as

$$-\Big[P(\tilde{x}) A^T(x) + M^T(x) B^T(x) $$
$$+ A(x) P(\tilde{x}) + B(x) M(x) \qquad (32)$$
$$- \sum_{k \in \Gamma} \frac{\partial P(\tilde{x})}{\partial x_k} \big[A_k(x) x \big] \Big] > 0.$$

It is known that if the condition (15) holds with $\varepsilon_1(x) > 0$ for $x \neq 0$, because $v^T\big(P(\tilde{x}) - \varepsilon_1(x)I\big)v$ is an SOS, it is clear that $P(\tilde{x}) - \varepsilon_1(x)I \geq 0$ that results in $P(\tilde{x}) > 0$. This $P^{-1}(\tilde{x})$ is the invertible matrix of $P(\tilde{x})$ and $P(\tilde{x}) > 0$ so that $P^{-1}(\tilde{x}) > 0$. Therefore, $V(x) > 0$ can be achieved when $P^{-1}(\tilde{x}) > 0$. From (32), it is obvious that the condition (32) is equivalent to the condition (16) of Theorem 1. It means that if the condition (16) holds with $\varepsilon_2(x) > 0$ for $x \neq 0$, it leads to $\dot{V}(x) < 0$. Therefore, the system (8) is asymptotically stable at the zero equilibrium. The proof is certainly completed.

Theorem 1 gives an SOS-based solution for the controller design. Generally, equation (17) gives an appropriate controller gain $K(x)$ if $P(\tilde{x})$ and $M(x)$ can be found. Subsequently, we attempt to solve the conditions of Theorem 1 for the HIV model (8) and its parameters in Table 1 using the Sum of Squares Optimization Toolbox (SOSTOOLS) in Matlab. Unfortunately, the feasible solutions for $P(\tilde{x})$ and $M(x)$ to satisfy those conditions cannot be found. In order to resolve the infeasible solutions problem, the conditions in Theorem 1 must be relaxed. Let us define

$$\Phi(x) = P(\tilde{x}) A^T(x) + M^T(x) B^T(x) + A(x) P(\tilde{x})$$
$$+ B(x) M(x) - \sum_{k \in \Gamma} \frac{\partial P(\tilde{x})}{\partial x_k} \big[A_k(x) x \big] \qquad (33)$$

and if $-\Phi(x) > 0$, that means

$$x^T \Phi(x) x < 0. \qquad (34)$$

According to the Finsler's Theorem ([21] and [22]), (34) holds with a polynomial matrix $U(x)$ satisfying $U(x)x = 0$ for all $x \neq 0$ is equivalent to

$$\Phi(x) + G^T(x) U(x) + U^T(x) G(x) < 0 \qquad (35)$$

for a certain matrix $G(x)$. From (16) and (35), it yields

$$-v^T \Big(P(\tilde{x}) A^T(x) + M^T(x) B^T(x) + A(x) P(\tilde{x})$$
$$+ B(x) M(x) - \sum_{k \in \Gamma} \frac{\partial P(\tilde{x})}{\partial x_k} \big[A_k(x) x \big] \qquad (36)$$
$$+ G^T(x) U(x) + U^T(x) G(x) + \varepsilon_2(x) I \Big) v$$

is an SOS.

Remark 1: Note that the polynomial matrix inequality (35) holds, (16) can be relaxed to be the condition (36) which will help us much easier to design the controller (12) for the HIV model (8). Only according to the conditions (15) and (16) are infeasible to solve directly the solutions of $P(\tilde{x})$ and $M(x)$, thereby, we have to hold a new condition (36) to upgrade the original theoretical basis of this paper to supply certain auxiliary calculation assistances. Since it may be much easier to find the polynomial matrices $P(\tilde{x})$ and $M(x)$ if we have chosen the appropriate polynomial matrices $U(x)$ and $G(x)$. In other words, because there are free variables $U(x)$ and $G(x)$ to be chosen such that we have more chance to find the feasible solution for $P(\tilde{x})$ and $M(x)$. The details are shown in the next design procedure.

Now, it is ready to summarize the following procedure to design the controller (12).

Step 1: Firstly, on the basis of the Finsler's Theorem [21] to select the matrix $U(x)$ such that $U(x)x = 0$ and choose a certain polynomial matrix $G(x)$.

Step 2: Solve the condition (36) to find the matrices $P(\tilde{x})$ and $M(x)$. If $P(\tilde{x})$ and $M(x)$ are infeasible, return to Step 1 to find another $U(x)$ and $G(x)$, and try again.

Step 3: Find $K(x)$ from (17) and then the controller (12) is synthesized.

IV. EXPERIMENTAL SIMULATION

To simulate the dynamics of CD4+T cells, CD8+T cells and viral load of the system with the model (8). The physical descriptions of the parameters are shown in detail in Table 1. Note that $0 < \bar{x}_1 < x_{10}$, $\bar{x}_2 > x_{20}$ and $\bar{x}_3 \geq 0$. The final target is to construct a controller for drug dosage in the antiretroviral therapy. Suppose we choose

$$U(x) = 10^{-1} \begin{bmatrix} 2x_1 x_2^2 x_3^2 & -x_1^2 x_2 x_3^2 & -x_1^2 x_2^2 x_3 \end{bmatrix}, \qquad (37)$$

$$G(x) = \begin{bmatrix} 2x_1 x_2^2 x_3^2 & -x_1^2 x_2 x_3^2 & -x_1^2 x_2^2 x_3 \end{bmatrix}. \qquad (38)$$

Then, solve (36) by using the Toolbox (SOSTOOLS), we have

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$$M(x) = \begin{bmatrix} m_{11} & m_{12} & m_{13} \end{bmatrix}, \ P(\tilde{x}) = \begin{bmatrix} p_{11} & p_{12} & p_{13} \\ p_{21} & p_{22} & p_{23} \\ p_{31} & p_{32} & p_{33} \end{bmatrix} \quad (39)$$

where

$$\begin{aligned} m_{11} = &-7.531e^{-2}x_1^2 + 5.163e^{-2}x_1x_2 + 0.1862x_1x_3 \\ &+ 1.797e^{-2}x_1 - 0.6939x_2^2 - 0.1853x_2x_3 \\ &+ 2.053e^{-2}x_2 - 6.608e^{-5}x_3^2 + 1.695e^{-2}x_3 - 1.087, \end{aligned}$$

$$\begin{aligned} m_{12} = &\ 8.313e^{-3}x_1^2 - 5.709e^{-3}x_1x_2 - 2.062e^{-2}x_1x_3 \\ &- 1.167e^{-2}x_1 + 7.634e^{-2}x_2^2 + 2.092e^{-2}x_2x_3 \\ &+ 0.1639x_2 + 1.276e^{-6}x_3^2 + 1.8e^{-2}x_3 + 0.1196, \end{aligned}$$

$$\begin{aligned} m_{13} = &\ 0.8655x_1^2 + 2.671e^{-3}x_1x_2 + 0.2602x_1x_3 \\ &+ 4.136e^{-3}x_1 + 0.6324x_2^2 - 0.1002x_2x_3 \\ &+ 1.454e^{-4}x_2 + 0.5219x_3^2 + 2.938e^{-3}x_3 + 0.4791. \end{aligned}$$

and

$$\begin{aligned} p_{11} = &\ 3.83e^{-5}x_1^2 + 6.379e^{-4}x_1x_2 - 6.333e^{-3}x_1 \\ &+ 2.952e^{-3}x_2^2 - 5.758e^{-2}x_2 + 0.8558, \end{aligned}$$

$$\begin{aligned} p_{22} = &\ 1.382e^{-6}x_1^2 + 1.476e^{-5}x_1x_2 - 1.041e^{-3}x_1 \\ &+ 7.569e^{-5}x_2^2 - 9.467e^{-3}x_2 + 2.131, \end{aligned}$$

$$\begin{aligned} p_{33} = &\ 5.819e^{-6}x_1^2 - 2.898e^{-7}x_1x_2 + 1.669e^{-7}x_1 \\ &+ 2.173e^{-5}x_2^2 + 1.362e^{-7}x_2 + 3.0e^{-5}, \end{aligned}$$

$$\begin{aligned} p_{12} = p_{21} = &-4.115e^{-6}x_1^2 - 6.957e^{-5}x_1x_2 + 5.646e^{-4}x_1 \\ &- 3.212e^{-4}x_2^2 + 5.133e^{-3}x_2 + 0.181, \end{aligned}$$

$$\begin{aligned} p_{13} = p_{31} = &\ 2.074e^{-6}x_1^2 + 1.142e^{-6}x_1x_2 + 2.863e^{-7}x_1 \\ &+ 2.614e^{-5}x_2^2 + 4.141e^{-7}x_2 + 1.784e^{-5}, \end{aligned}$$

$$\begin{aligned} p_{23} = p_{32} = &-2.288e^{-7}x_1^2 - 1.22e^{-7}x_1x_2 + 2.147e^{-7}x_1 \\ &- 2.878e^{-6}x_2^2 - 4.195e^{-6}x_2 - 2.31e^{-6}. \end{aligned}$$

From (39), we can obtain the controller parameter $K(x) = M(x)P^{-1}(\tilde{x})$ based on step 3.

Meanwhile, for real medical practice, the blood sample is extracted from the patient to measure antibody and virus on a weekly. Choose a suitable sampling time for the calculation and simulation. We shall set an initial condition as the long-term infected situation for the HIV model (8). Let the sampling time $T_s = 0.02$ be set in this simulation to stand for a week. From Fig. 1, it is seen that an infected person has not any drug therapy. Suppose at $t = 10$ in Fig. 1, we start to give the drug to the patient that means the designed controller is activated. In other words, the initial condition for the therapy initialization is set in the states of $t = 10$ in Fig. 1 where $x_{initial} = \begin{bmatrix} -524 & 176 & 0.005 \end{bmatrix}^T$.

In the practical therapeutic procedure, the adjustments of drug dosage are always dependent on the changes of viral load concentration in plasma of the patient. Especially, if the patient has accepted enough appropriate medical treatment, the count of viral load will drop to the undetectable level in a certain point-in-time of the entire clinical therapeutic process. With the aids of our designed controller, the simulation results are shown in the following figures.

Figure 2 shows that when the therapy starts x_1 ascends and finally reaches to zero asymptotically, x_2 also converges to zero finally. However, it is seen that both x_1 and x_2 need a long time-span to converge to zero when the proposed control (drug therapy) is applied. It is comprehensible because x_3 is always retained in the body, even with drug therapy in the rest of the life of the patient. In Fig. 3, the viral load x_3 descends rapidly to near zero state and finally remains in very little level, but it does not mean the patient is cured to be healthy since x_1 and x_2 are still not in healthy states. Additionally, the count of viral load x_3 is actually only reduced to an undetectable level, it means that the patient needs to accept drug therapy continuously along with the remaining life so that viral load x_3 will not recover to any detectable level.

Frankly speaking, in Fig. 4, it shows that the control u works efficiently in the entire therapy period. According to a universal awareness, if a patient accepts correct treatment after being infected for a period, the state of illness can be well controlled and approaches to health state asymptotically.
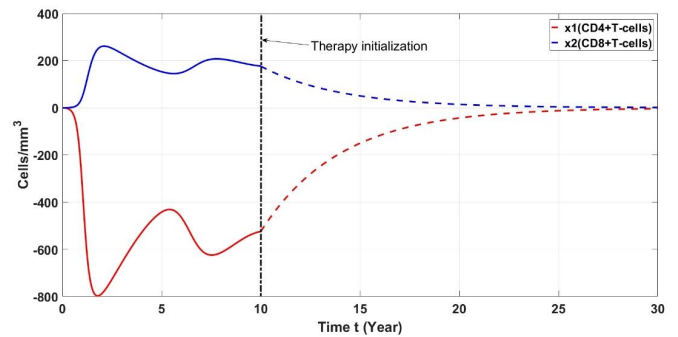
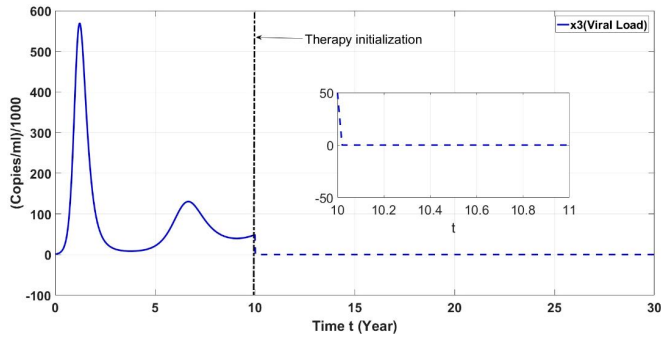

Figure 2. The state trajectories of x_1 and x_2.

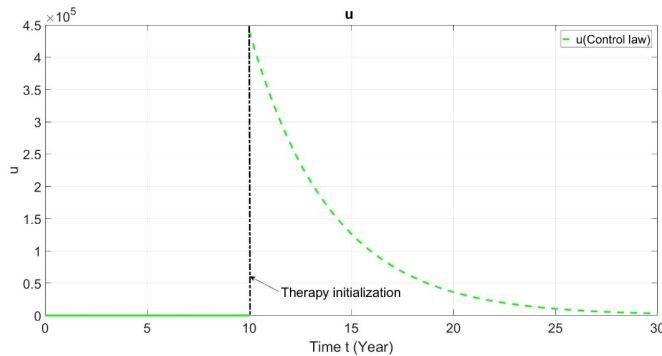**Figure 3.** The state trajectory of x_3.

Figure 4. The state trajectory of u

V. CONCLUSION

In this article, we use the proposed method to stabilize a model system of HIV infection. By exploiting the model properties, the original model system (1) is transformed into a new model system (7) via a simple mathematic transformation that will make us study it easily in the next stage. A high effective control law is designed based on the Lyapunov design and SOS technique, this is the most important section in this case because this proposed control design can help the state of the model system return to the desired values. By the control design to regulate and suppress HIV, the results also show the stability of the system.

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